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High heritability for a composite index of children's activity level measures

Alexis C. Wood¹, Frühling Rijsdijk¹, Kimberly J. Saudino², Philip Asherson¹, and Jonna Kuntsi¹

¹MRC Social, Genetic and developmental Psychiatry Centre, Institute of Psychiatry, Kings College London, De Crespigny Park, London, SE5 8AF, UK

²Psychology Department, Boston University, Boston, Massachusetts, USA.

Abstract

Despite the high heritability of children's activity level, which forms part of the core symptom domain of hyperactivity-impulsivity within attention deficit hyperactivity disorder (ADHD), there has only been a limited success with identifying candidate genes involved in its etiology. This may reflect a lack of understanding about the different measures used to define activity level across studies. We aimed to study the genetic and environmental etiology across three measures of activity level: parent and teacher ratings of hyperactivity-impulsivity and actigraph measurements, within a population-based sample of 463 7-9 year old twin pairs. We further examined ways in which the three measures could be combined for future molecular studies. Phenotypic correlations across measures were modest, but a common underlying phenotypic factor was highly heritable (92%); as was a simple aggregation of all three measurements (77%). This suggests that distilling what is common to all three measures may be a good method for generating a quantitative trait suitable for molecular studies of activity level in children. The high heritabilities found are encouraging in this respect.

Keywords

Activity level; heritability; actigraph; ADHD; rater effects

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is estimated to affect 3 – 10 % of children (Bird, Gould, & Staghezza, 1993; Faraone, Sergeant, Gilberg, & Biederman, 2003; Ford, Goodman, & Meltzer, 2003). It is characterized by developmentally inappropriate levels of over-activity, impulsivity and/or inattention. There has been moderate success in identifying candidate gene associations, in particular involving genetic variants within or near to the dopamine D4 and D5 receptor genes, although the effect sizes are small (Asherson, 2004; Faraone et al., 2005; Kuntsi, Neale, Chen, Faraone, & Asherson, 2006). In research into the genetic and environmental influences on ADHD both diagnostic (categorical) and quantitative trait loci (QTL) approaches have been adopted. The QTL approach considers ADHD as the extreme of one or more behaviours that vary continuously throughout the entire population and are influenced by multiple genetic variants, each likely to confer only relatively small effects when considered on their own.

Correspondence to: Miss A Wood, MRC Social, Genetic and Developmental Psychiatry Centre, PO Box 80, Kings College London, De Crespigny Park, London, SE5 8AF, UK. Telephone +44 (0)20 7848 5401. Fax +44 (0)20 7848 0866. Email: alexis.wood@iop.kcl.ac.uk.

In studies seeking to identify the etiology of ADHD behaviours, the 'activity level' phenotype is commonly defined by parent and teacher ratings taken from behavioural questionnaires. While behavioural rating scale data have many benefits as a source of information, this reliance may contribute to the limited success of molecular genetic studies seeking to identify genes involved in the etiology of activity level. Parent and teacher ratings of ADHD behaviours typically correlate at around .3 (Saudino, Ronald, & Plomin, 2005; Thapar, Harrington, Ross, & McGuffin, 2000). This low correlation has been attributed to many sources, including the situational specificity of the raters' experiences of the child, differential experiences of the child's peer group, and rater biases. For example, structural equation modeling suggests that the surprisingly low DZ correlations, often found in parent ratings, arise from contrast effects between DZ twins (Eaves et al., 2000; Saudino, Cherny, & Plomin, 2000; Simonoff et al., 1998). Although teacher ratings do not show the same form of rater bias, they may be subject to other forms such as 'halo effects', where their ratings of children's ADHD symptoms are affected by other behaviours of the child, particularly those associated with conduct disorder or oppositional defiant disorder (Abikoff, Courtney, Pelham, & Koplewicz, 1993; Schachar, Sandberg, & Rutter, 1986; Stevens, Quittner, & Abikoff, 1998). Different biases may have different effects on heritability estimates. When not accounted for, contrast effects may result in the over estimation of heritability, or the detection of dominance. Halo effects will, however, result in an over-estimation of shared environmental influences.

Parent and teacher ratings can show significantly different heritability estimates, with parent ratings often showing higher heritability estimates than teacher ratings (Eaves et al., 1997; Goodman & Stevenson, 1989; Kuntsi & Stevenson, 2001), although this is not always the case, especially when both members of a twin pair are rated by the same teacher (Martin, Scourfield, & McGuffin, 2002; Saudino, Ronald, & Plomin, 2005). Regardless of individual heritabilities, both measures often show significant rater-specific genetic effects (Martin, Scourfield, & McGuffin, 2002; Nadder, Silberg, Rutter, Maes, & Eaves, 2001; Thapar, Harrington, Ross, & McGuffin, 2000), and can be problematic when phenotype definition may be crucial for success in molecular genetic studies (Holmes et al., 2002). The importance of aggregating scores across measures to reduce rater-specific effects has previously been shown, which may help maximise sensitivity to the underlying genotype (DuPaul, 2003; Martin, Scourfield, & McGuffin, 2002; Rothbart & Hwang, 2002; Saudino, 2002; Sherman, McGue, & Iacono, 1997; Tripp, Schaughency, & Clarke, 2006).

Actigraphs, which measure movement in an objective and quantifiable way, offer a method of measuring activity level directly. Therefore, they may help to distinguish activity level from the other components of the ADHD phenotype. Although actigraph data may be more time consuming to collect compared to questionnaire data, they provide technologically simple, objective activity level data (Eaton, McKeen, & Saudino, 1996), in a method that can be used over large periods of time and has been shown to be readily accepted by the majority of young people (Van Coevering et al., 2005). Motion sensor data show good discrimination between ADHD and comparison groups (Inoue et al., 1998; McGrath, Handwerk, Armstrong, Lucas, & Friman, 2004; Teicher, Ito, Glod, & Barber, 1996), having indicated an activity level that is 25 – 30% higher in children with ADHD compared to controls (Porrino et al., 1983). Actigraphs can also detect changes in motor activity following drug treatment for ADHD (Porrino, Rapoport, Behar, Ismond, & Bunney, 1983), although this can be dependent on circumstances, with situations requiring greater self regulation having the most discriminatory power (Dane, Schachar, & Tannock, 2000).

Recent studies suggest promise for the inclusion of actigraphs in behavioural genetic studies, with twin correlations suggesting heritabilities of around 40% for actigraph data collected on both children and adults (Saudino & Eaton, 1991; Spinath, Wolf, Angleitner, Borkenau, &

Riemann, 2002). Although the role of shared environmental influences differs across studies, the same genetic influences have been shown to influence motor activity as measured by actigraphs in different experimental situations (Wood, Saudino, Rogers, Asherson, & Kuntsi, 2007). One study also reported a positive correlation between the number of 7-repeat alleles in DRD4 and actigraph-measured activity level (Langley et al., 2004), a genetic variant also associated with a small estimated odds ratio of 1.4-1.9 in ADHD (Faraone, Doyle, Mick & Beiderman, 2001).

Despite this, the place of actigraphs in a multi-modal assessment of children's activity level remains unclear, and a key outstanding issue is to provide an understanding of the covariation of more subjective observer-rated data with the direct measure of behaviour given by actigraph data (Goldsmith & Hewitt, 2003). Studies using actigraphs find a similar degree of phenotypic overlap between mechanical data and behavioural measures as there is between parent and teacher rated data, with general population actigraph scores correlating with parent ratings on the Child Behaviour Questionnaire at between .23 and .26 (Saudino, Wertz, Gagne, & Chawla, 2004), which is similar to previous actometer findings (Goldsmith & Hewitt, 2003). However, correlation co-efficients can be dependent on the rating scale used (Saudino, Wertz, Gagne, & Chawla, 2004), emphasising the need for further investigation into how the conceptualisation of activity level, or 'hyperactivity' – a construct that can include measures of inattention and impulsivity – assessed from questionnaire data co-varies with mechanical data.

To our knowledge, quantitative genetic studies have yet to address the etiological links between actigraph measures and parent and teacher ratings of activity level. This study aims to investigate the phenotypic and etiological overlap between actigraph measurements and ratings of hyperactivity-impulsivity from parents and teachers taken in middle childhood, on a sample of 486 twin pairs between 7 and 9 years of age. We further aimed to investigate potential ways that these three measures could be combined for use in future molecular genetic studies.

METHODS AND MATERIALS

Sample

Participants are members of the Study of Activity and Impulsivity Levels in children (SAIL), a general population sample of twins at age 7 to 9 years. The sample was recruited from a birth cohort study, the Twins' Early Development Study (TEDS; Trouton, Spinath, & Plomin, 2002), which had invited parents of all twins born in England and Wales during 1994-1996 to enroll. Despite attrition, the TEDS families continue to be fairly representative of the UK population with respect to parental occupation, education and ethnicity (Spinath & O'Connor, 2003). Zygosity has been determined using a standard zygosity questionnaire, which has been shown to have 95% accuracy when compared to zygosity status determined by genotype data (Price et al., 2000).

Families on the TEDS register were invited to take part if they fulfilled the following SAIL project inclusion criteria: twins' birthdates between 1st September 1995 and 31st December 1996; lived within feasible traveling distance of the Research Centre (return day trip); ethnic origin white European (to reduce population heterogeneity for molecular genetic studies); recent participation in TEDS, as indicated by return of questionnaires at either 4- or 7-year data collection point; no extreme pregnancy or perinatal difficulties (15 pairs excluded), specific medical syndromes, chromosomal anomalies (two pairs excluded) or epilepsy (one pair excluded); not participating in other current TEDS sub-studies (45 pairs excluded); and not on stimulant or other neuropsychiatric medications (two pairs excluded).

The current analyses focus on data obtained following contact with the first 1,230 suitable families on the register. Of these, 672 families agreed to participate, reflecting a participation rate of 55%. Actigraph data were obtained for 486 families and, of the 972 participants, data from twenty-two individual children were subsequently excluded (thirteen children with IQs below 70, three children due to epilepsy and one child due to each of the following: obsessive-compulsive disorder, neurofibromatosis, hyperthyroidism, dyspraxia, severe autism and on stimulant medication for ADHD). In addition, data from 108 participants were lost due to mechanical failure and data from six participants were subsequently excluded due to difficulties during test sessions that inappropriately affected the data (e.g. playing with the actigraph). These data were considered 'missing at random' and those who lost actigraph data did not differ from those who did not in terms of either parent ($t_{1296}=-0.28$; $p=0.78$) or teacher ($t_{1152}=0.38$; $p=0.70$) ratings of hyperactivity-impulsivity.

The final sample consisted of 836 children (403 males and 433 females); 325 identical (monozygotic, MZ) twins (data for 150 complete twin pairs), 253 same-sex non-identical (dizygotic, DZ) twins (data for 113 complete twin pairs) and 258 opposite-sex DZ twins (111 complete twin pairs). The data for the remaining 88 'singleton' twins were also used for model fitting in the structural equation modeling (see M. C. Neale, Boker, Xie, & Maes, 2006). The mean age was 8.51 years ($SD = 0.42$). Parents of all participants have given informed consent and the Institute of Psychiatry Ethical Committee approved the study.

Measures

Actigraph measurements—The families visited the Research Centre for the actigraph assessments (for further details see Wood, Saudino, Rogers, Asherson, & Kuntsi, 2007). Actigraph readings reflecting the cumulative intensity of movement were taken from the dominant leg and waist during two situations; a laboratory-based test session, when the twins were apart completing a short-form IQ test and several theory-driven experimental tasks (see Kuntsi et al., 2006), and a 25-minute unstructured break when twins were together. The total length of the testing session, including break, was approximately 2.5 hours.

Previous analyses showed that over the whole session, including the laboratory-based testing and the break, the two actigraph measurements taken on the leg and waist were significantly correlated at $r = 0.52$ ($p < 0.001$), and the same genetic influences underlay actigraph data in the two situations (Wood, Saudino, Rogers, Asherson, & Kuntsi, 2007). Therefore a mean actigraph score was used which represents the average cumulative frequency per minute, averaged across limbs and across situations, to give one actigraph measurement per child, over the whole session.

Ratings of hyperactivity-impulsivity—Parents were asked to complete the Long Version of the Conners' Parent Rating Scale (CPRS-R:L; Conners, Sitarenios, Parker, & Epstein, 1998a) and teachers the Long Version of the Conners' Teacher Rating Scale (CTRS-R:L; Conners, Sitarenios, Parker, & Epstein, 1998b). Ratings were completed by the primary caregiver, which for the majority was the mother. Teacher data was completed by the main class teacher for each child. In a few cases, missing data in Conners' scales were pro-rated, where a summary score based on the mean of individual questions on the rest of the subscale was used, if there was more than 75% completion for each subscale. Of those with actigraph data ($N=836$) 832 had Conners' Parent Rating Scale data available, and 762 had Conners' Teacher Rating Scale data.

Analyses

The structural equation-modeling program Mx (Neale, Boker, Xie, & Maes, 2006) was used to conduct the genetic analyses and confirmatory phenotypic factor analysis and correlations. Models were fitted to age- and sex-regressed residual scores, using raw data analysis. Participants with incomplete data were included in the analyses as Mx provides a method for handling incomplete data by using raw maximum likelihood estimation, in which a likelihood statistic (-2LL) of the data for each observation is calculated. The fit of restricted models is assessed by a likelihood ratio χ^2 test, where the difference between -2LL of the full and restricted model is distributed as a χ^2 with the degrees of freedom (df) equal to the difference between the number of parameters estimated between the two models. When likelihood ratio tests cannot be applied, the AIC index (χ^2-2df) is used to indicate which model has more support (Williams & Holahan, 1994).

Phenotypic analyses

Phenotypic factor model (figure I): A confirmatory factor model is used to confirm that a common phenotypic factor will explain a significant proportion of the variance of each measure of activity level (actigraph measurements, parent ratings of hyperactivity-impulsivity and teacher ratings of hyperactivity-impulsivity). In the model, the variance of each measure is partitioned into that which is shared between the measures (the common factor) and the residual, unshared variance (residual variance, RV). The squared loading of each measurement on the common factor represents the amount of variance of each individual measure of activity level that is attributed to the common factor. To account for the relatedness of the individuals in the sample, separate factors are fitted for measures of twin 1 and measures of twin 2, and these factors are allowed to correlate. The residual factors for each measure are allowed to correlate across twins as well, to allow for twin correlations that are not due to the factor structure across twins. The factor loadings and residual errors are equated across twins and zygosity groups for each measure of activity level, such that the same factor model is specified across twins in a pair and across zygosity groups. However, as there may be a genetic influence to the covariation across the three measures, or to the variation in factor scores, the correlation between factors, and the correlations between residual variances are allowed to vary across the different zygosity groups. This factor model is compared to the fully saturated phenotypic model to see if imposing a common latent factor to explain the covariation in measures results in a significant drop in fit. Nested models, where the loadings of measures on the factor can be equated or dropped, are compared to the full factor model.

Univariate genetic models—Univariate genetic analyses use twin correlations for each trait, and on the basis that MZ twins share 100% of their segregating alleles, DZ twins 50% of additive genetic influences and 25% of non-additive genetic influences, partition the phenotypic variance of the measures into additive genetic (A), dominance (D) or shared environmental (C), and child specific environmental (E) effects. Any possible measurement error is subsumed under the E effects (Rijsdijk & Sham, 2002).

Multivariate genetic models

Cholesky model with correlated factors solution (figure II): Multivariate genetic analyses allow us to investigate whether the same genetic and environmental factors influence activity level across the three measures. In multivariate twin analysis, MZ and DZ correlations are compared across traits: that is, one twin's score on a trait is correlated with the co-twin's score on another trait. Here, the three traits represent the three different measures of activity level. If cross-trait twin correlations are greater for MZ than for DZ twins, this implies that genetic factors contribute to the covariation across traits. A genetic

correlation (r_A) indicates the extent to which genetic influences on one trait overlap with those on another trait (regardless of their individual heritabilities). Correlations can similarly be estimated for shared environmental influences (r_C) and for child-specific environmental influences (r_E). Based on the individual heritability of each trait, and the estimated genetic correlation, the proportion of the phenotypic correlations that is due to genetic influences can also be calculated. As the Cholesky allows the first latent variable in each etiological factor group to affect all measured variables, but the second latent variable is uncorrelated with first and only affects the second measured variable and beyond (a pattern that is repeated for all latent variables), to avoid giving any one latent variable precedence over the others, a correlated factor solution of the Cholesky model is interpreted (figure II). The correlated factor solution is mathematically equivalent to the Cholesky (Loehlin, 1996); all measures have separate A, C and E influences to account for their variance and the correlations across these influences across measures are estimated.

Common pathway model (figure III): The common pathway model represents the covariation among measures as a latent phenotype, much like the phenotypic factor model. The loadings of each measure on the latent phenotype are estimated and the variance in the latent phenotype is divided into the components A, C and E. The residual variance in each measure, i.e. that variance which is not due to the latent phenotype but unique to each measurement, is also divided into A, C and E factors. This fit of the model is compared to that of the Cholesky model, to see if there is a significant drop in fit by imposing a common pathway model.

RESULTS

Phenotypic analyses

Confirmatory Phenotypic factor model between actigraph measurements and parent and teacher ratings of hyperactivity-impulsivity (Figure I)—The likelihood of a one factor model, compared to that of the fully saturated phenotypic model, indicated a good fit to the data ($\chi^2=38.97$, $df=28$, $p=0.08$), suggesting that one common factor underlies all three measures of activity level. The common factor explained 35% of the variance in parent ratings of hyperactivity-impulsivity, 30% of the variance in teacher ratings of hyperactivity-impulsivity and 10% of the variance in actigraph measurements. The loadings of the questionnaire measures on the common factor could be equated without a significant drop in fit ($\chi^2=0.48$, $df=1$, $p=0.49$). Although the actigraph measurements contributed significantly less to the measurement of the common factor, they could not be dropped from the model ($\chi^2=35.57$, $df=1$, $p<0.001$), suggesting all measures contribute significantly to the latent trait.

Genetic analyses

In all cases, to avoid artificially inflating parameters, estimates (with 95% confidence intervals) are provided from full models, and non-significance is indicated by 95% confidence intervals that include 0.

Univariate analyses of a composite of all three measurements of activity level

—A mean was taken of the three transformed and age- and sex-regressed measures of activity level (actigraph measurements, parent ratings and teacher ratings) to form a composite activity-level measure. MZ correlations were higher than DZ correlations (Table I), indicating a genetic influence to the phenotype. The univariate model fitting results are presented in Table II. According to the full model, the proportion of variance (95% confidence intervals in brackets) accounted for by A was 77% (55-84%), by C 1% (0-22%) and by E 21% (16-27%).

Multivariate genetic models within and -between actigraph measurements and parent and teacher ratings of hyperactivity-impulsivity—

As assumed by the genetic model, the phenotypic and twin correlations are presented from a constrained model, where phenotypic correlations across twin 1 and twin 2 and across zygosity are equated. All measures were significantly correlated, and MZ correlations were higher than DZ correlations for all measures (Table I) suggesting genetic contributions to each measure.

For the parent ratings of hyperactivity-impulsivity, the MZ correlations were more than twice the DZ correlations (Table I), and there were non-significant MZ and DZ variance differences ($p=0.65$) indicating that an ADE would be the best fit to the data (Rietveld, Posthuma, Dolan, & Boomsma, 2003); this was reflected in the univariate modeling. However, fitting an ADE model in a multivariate model with other phenotypes that best fit an ACE model can be problematic, as we are unlikely to have the power to distinguish between A and D and given that D and C are conflated. Thus an ACE model was fitted in the multivariate analyses which resulted in the same estimates for overall heritability and E parameters as in the ADE univariate model. However, this resulted in a drop in fit for the multivariate models, with the multivariate models being a worse fit when compared to the fully saturated model (Table II), whereas the individual univariate models were not.

Table II provides the model fitting results for the multivariate models. Table III and Figure II present parameter estimates from the full correlated factor solution of the Cholesky model. The heritability of each variable is given in bold on the diagonal in the top third of the table, with 95% confidence intervals in brackets (e.g. the heritability of actigraph measurements was 35%). The genetic correlation between the pairs of variables is given below the diagonal, with 95% confidence intervals in brackets (e.g. the genetic correlation between parent and teacher ratings of hyperactivity-impulsivity was .48). The contribution of genetic factors to the phenotypic correlation between variables, with the percentage of the phenotypic correlation that is due to genetic effects in brackets, is given above the diagonal (e.g. the contribution of genetics to the phenotypic correlation between parent ratings of hyperactivity-impulsivity and actigraph measurements was .20, which accounted for 95% of the phenotypic correlation). The same three types of information are presented for the variance components C and E in the second and third sections of the table, respectively.

The common pathway model did not present a significant drop in fit compared to the Cholesky model (Table II). The latent trait had a heritability of 92% (73-100%), with the remaining 8% of the variance being accounted for by child-specific environment and possible measurement error. The latent trait loaded onto all three measures of activity level significantly, in accordance with the phenotypic model (Table II, Figure III), explaining 10% (4-18%) of the variance in actigraph measurements, 42% (25-73%) in parent ratings of activity level and 27% (14-43%) in teacher ratings of activity level. Any variance in measures not accounted for by the latent phenotype was due to measurement-specific etiological factors (Table III, Figure III).

DISCUSSION

We report a modest, but significant phenotypic overlap between three measures of activity level (actigraph measurements, and parent and teacher ratings of hyperactivity-impulsivity). All three measures had both shared and unique genetic and environmental influences, and all contributed significantly to a highly heritable latent trait. The phenotypic overlap between the parent and teacher ratings of hyperactivity-impulsivity and between parent ratings and actigraph measurements were as expected from previous studies, at 0.3 and 0.2 respectively (Goldsmith & Hewitt, 2003; Saudino, Ronald, & Plomin, 2005; Saudino, Wertz, Gagne, & Chawla, 2004; Thapar, Harrington, Ross, & McGuffin, 2000). In addition, we found the

correlation between teacher ratings and actigraph measurements to be 0.2 and therefore of the same magnitude as for parent-rated data. Although the phenotypic correlations were low, all measurements contributed significantly to a highly heritable latent phenotypic trait.

Our data confirm the expected heritability of both actigraph measurements at 36% (see Wood, Saudino, Rogers, Asherson, & Kuntsi, 2007 for more detail) and parent ratings of hyperactivity-impulsivity (77% with the rest of the variance being due to E). In line with some previous findings (Foley et al., 2004; Goodman & Stevenson, 1989; Kuntsi & Stevenson, 2001) we report a lower heritability for teacher ratings (41%), with no significant role for C. The lack of overlapping 95% confidence intervals adds weight to the body of evidence that reports significantly different effect sizes for genetics in the etiology of parent and teacher ratings of ADHD symptoms (Eaves et al., 1997; Goodman & Stevenson, 1989; Kuntsi, Oosterlaan, & Stevenson, 2001) and emphasises the need for a better understanding of the differences in the measures of activity level by different raters.

The genetic correlation between parent and teacher ratings of hyperactivity-impulsivity was estimated to be 0.48, suggesting that around half the genes influencing parent ratings of hyperactivity-impulsivity also influence teacher ratings. These data also confirm the finding that there are both shared and unique (rater-specific) genetic influences (Martin, Scourfield, & McGuffin, 2002; Nadder, Silberg, Rutter, Maes, & Eaves, 2001; Thapar, Harrington, Ross, & McGuffin, 2000). Similarly, between parent ratings and actigraph measurements the genetic correlation was estimated as 0.39, again suggesting the presence of both shared and unique genetic influences. Furthermore, genetic effects drove 95% of the covariation between the parent ratings and actigraph data, 42% of covariation between teacher ratings and actigraph data and 84% of covariation between parent and teacher ratings. Altogether these data suggest that extracting what is common to the measures, and removing measurement and rater-specific effects, will generate a quantitative trait that best represents the shared genetic effects that influence all three measures and might therefore be suitable for molecular genetic studies, where identifying homogeneous phenotypes may be crucial for success (Holmes et al., 2002).

The mean of all three measures of activity level showed a high heritability of 77%, with the remaining variance mostly due to child-specific environmental effects and measurement error (21%). In examining more complex ways to combine the three measures, extracting an underlying latent trait common to all three measures provided a good fit to the data. This trait was highly heritable, with 92% of the variance being due to additive genetic factors and the remaining 8% to child-specific environment plus measurement error. These results indicate that both measurement-specific biases and errors can be aggregated out of assessments of activity level.

The very high heritability of the latent trait for activity levels indicates the importance of genetic rather than familial environmental effects on the behavioural phenotype, and is therefore of importance to clinicians seeking to understand the origins of overactive behaviour and the aggregation of such behavioural patterns within families (Gjone, Stevenson, & Sundet, 1996). Yet environmental influences may still have important roles to play, acting through mechanisms of gene by environment interactions. The existence of considerable specific genetic effects on the various measures of activity level further highlights the importance of the distinction between situation-pervasive and situation-specific behaviours in diagnostic practice (Sherman, McGue, & Iacono, 1997).

Actigraph data were collected at a Research Centre to ensure comparability of the assessment situation across twins and families. It is yet to be explored how actigraph measurements in different situations overlap etiologically with parent and teacher ratings of

activity level. Although previous analyses suggest that the genes underlying actigraph data in different situations are similar, environmental effects may differ across situations (Wood, Saudino, Rogers, Asherson, & Kuntsi, 2007).

Despite modest inter-rater correlations between parent ratings, teacher ratings and actigraph measures of activity level, and the presence of measurement-specific contributions to each measure, we demonstrated that a common set of genes contributes to their co-variation, defining a highly heritable latent trait of activity level. Since a substantial portion of the covariation could be attributed to genetic effects, we suggest that combining data across measures may increase the power to detect genes in molecular genetic studies by reducing rater-specific factors and measurement-specific error.

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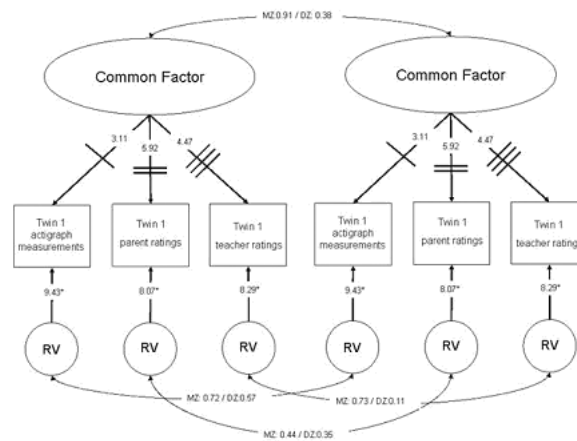
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*Residual variances are equated in the same manner across variables as factor loadings, but are not depicted in diagram for simplicity.

Lines in bold represent parameters equated across zygosity.

Figure I.
Phenotypic factor model for actigraph measurements and parent and teacher ratings of hyperactivity-impulsivity

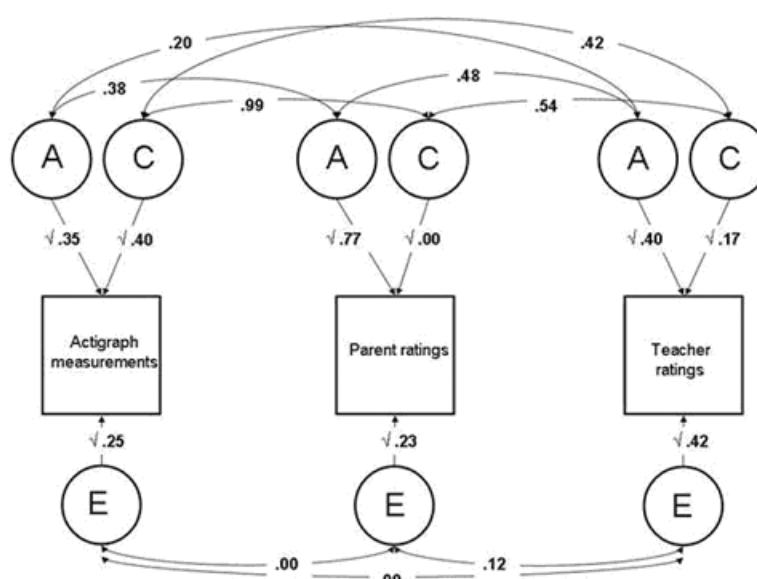


Figure II.
Standardised solution of the full Cholesky model (correlated factor solution presented)

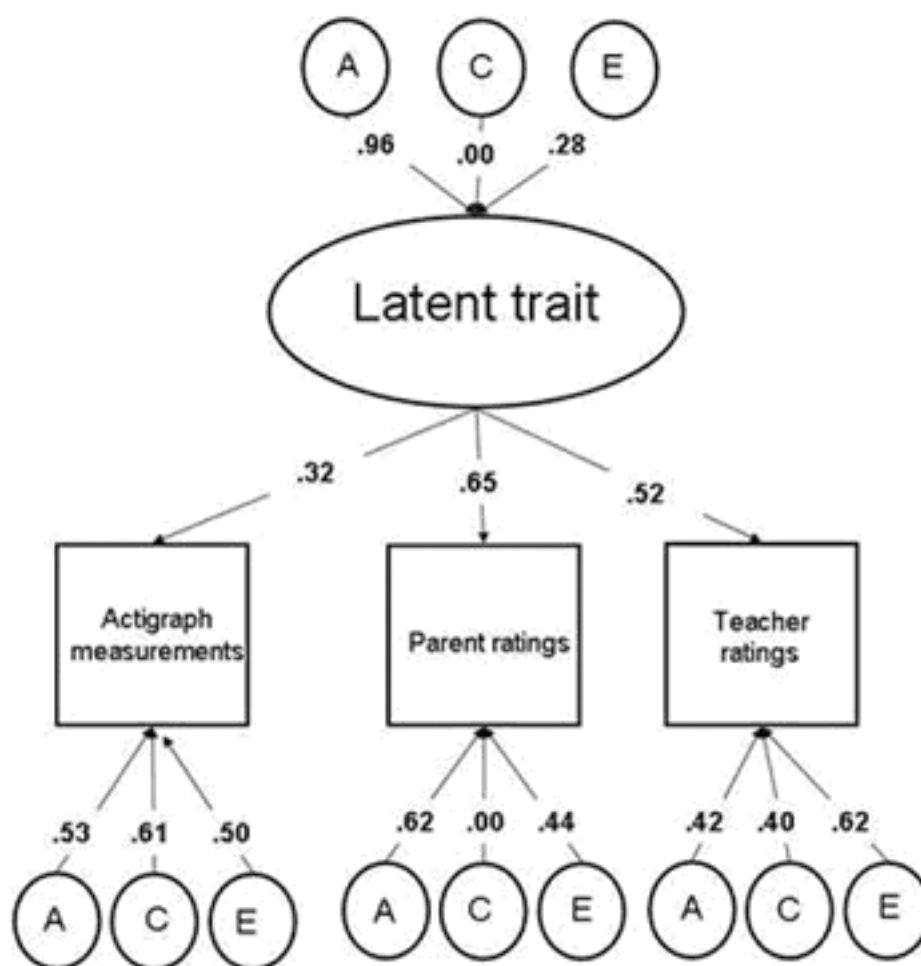


Figure III.
Unstandardised solution of full common pathway model

Phenotypic and within-pair correlations (95% confidence intervals in brackets) and means (standard deviations in brackets) for and across actigraph measurements and parent and teacher ratings of hyperactivity-impulsivity from the constrained, saturated model

TABLE 1

	Actigraph measurements	Parent ratings	Teacher ratings	Average of measures ^a
Actigraph measurements	1.00			
Parent ratings	0.22 (0.14-0.29)	1.00		
Teacher ratings	0.18 (0.10-0.25)	0.32 (0.25-0.39)	1.00	
<hr/>				
MZ Mean (SD)	337.45 (198.48) ^b	5.74 (4.76) ^c	2.40 (3.39) ^c	0.20 (0.96) ^d
DZ Mean (SD)	350.81 (247.88) ^b	6.30 (5.40) ^c	3.82 (5.27) ^c	-0.25 (1.02) ^d
<hr/>				
	Twin 1	Twin 1	Twin 1	Twin 1
	Actigraph measurements	Parent ratings	Teacher ratings	Average of measures ^a
	MZ DZ	MZ DZ	MZ DZ	MZ DZ
Twin 2 Actigraph measurements	0.72 (0.63-0.78)			
	0.58 (0.49-0.66)			
Twin 2 Parent ratings	0.22 (0.13-0.29)	0.78 (0.71-0.83)		
	0.10 (0.00-0.18)	0.18 (0.05-0.31)		
Twin 2 Teacher ratings	0.18 (0.09-0.26)	0.27 (0.18-0.35)	0.58 (0.46-0.68)	
	0.13 (0.04-0.22)	0.09 (-0.01 - 0.18)	0.34 (0.22-0.46)	
Twin 2 Average of measures ^a				0.78 (0.71-0.84)
				0.40 (0.28-0.51)

Note: MZ data in bold; DZ data in italic typeface.

^a Mean of actigraph composite, parent ratings of hyperactivity-impulsivity and teacher ratings of hyperactivity-impulsivity

^b Untransformed data

^c Untransformed, pro-rated scores

^d Composite taken of transformed, regressed and standardized scores.

Table II

Model fitting results of univariate genetic analyses of the mean activity measure and multivariate genetic analyses of actigraph measurements, parent ratings of hyperactivity-impulsivity and teacher ratings of hyperactivity-impulsivity.

Model	-2LL	df	χ^2	df	p	$\Delta\chi^2$	Δdf	p	AIC	Comparison Model
Univariate models of the mean of three 'activity level' measures										
1. Saturated model	1459.72	751	-	-	-	-	-	-	-	
2. ACE model	1461.89	754	2.17	3	0.54	-	-	-	-3.83	1
3. CE model	1503.65	755	43.59	4	<0.001	41.76	1	<0.001	35.59	1/2
4. AE model	1461.90	755	2.18	4	0.54	0.02	1	0.90	-5.82	1/2
5. E model	1627.23	756	167.51	5	<0.001	165.34	2	<0.001	157.51	1/2
Multivariate models										
1. Saturated model	17453.79	2373	-	-	-	-	-	-	-	
2. Cholesky	17498.53	2397	44.74	24	0.006	-	-	-	-3.26	1
3. Common Pathway	17504.25	2401	50.46	28	0.006	5.72	4	0.22	-5.54	2

Best fitting model indicated in bold. 2LL = Likelihood Statistic. AIC = Akaike's information criteria

Table III

Standardised Parameter estimates from the full correlated factors solution of the Cholesky model, and the full common pathway model

	Actigraph Measurements	Parent ratings	Teacher ratings
<u>Cholesky model^a</u>			
Genetic Influences			
Actigraph measurements	.35 (.16-.55)	.20 (95%)	.08 (42%)
Parent ratings	.39 (.16-.69)	.77 (.69-.82)	.27 (84%)
Teacher Ratings	.21 (-.29-.77)	.48 (.28-.88)	.40 (.11-.64)
Shared environment influences			
Actigraph measurements	.40 (.22-.55)	.00 (0%)	.11 (58%)
Parent ratings	.99 (-1.00 - +1.00)	.00 (.00-.05)	.00 (0%)
Teacher Ratings	.42 (-0.21- +1.00)	.54 (-1.00 - +1.00)	.17 (.00-.40)
Child specific environment influences			
Actigraph measurements	.25 (.20-.33)	.01 (5%)	.00 (0%)
Parent ratings	.02 (-0.18- +0.15)	.23 (.17-.30)	.05 (16%)
Teacher Ratings	.00 (-.16 - +.16)	.18 (.01-.33)	.42 (.33-.54)
<u>Common pathway model</u>			
Specific variance components			
a ²	.28 (.09-.48)	.39 (.09-.56)	.18 (.00-.48)
c ²	.37 (.19-.52)	.00 (.00 - .05)	.16 (.00-.37)
e ²	.25 (.20-.33)	.19 (.11-.27)	.39 (.30-.51)
Squared factor loadings ^b	.10 (.04-.18)	.42 (.25-.73)	.27 (.14-.43)

^aFor the Cholesky model the heritability (with 95% confidence intervals) of each variable is given in bold on the diagonal. The genetic correlations between the pairs of variables with 95% confidence intervals) are given below the diagonal. The contribution of genetic factors to the phenotypic correlation between variables, is given above the diagonal, with the percentage of the phenotypic correlation that is due to genetic effects in brackets. The same three types of information are presented for shared environmental and child-specific environmental influences.

^bThe latent phenotype has variance components with parameter estimates of $a^2 = 0.92$, $c^2 = 0.00$ $e^2 = 0.08$